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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/053,535 | 01/15/2002 | Augustine M. Choi | 13681-003002 | 7091 |

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EXAMINER

CHOI, FRANK I

/ ART UNIT PAPER NUMBER

1616

DATE MAILED: 03/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.A.M.

Office Action Summary**Application No.**

10/053,535

Applicant(s)

CHOI ET AL.

Examiner

Frank I Choi

Art Unit

1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 42-47, 50 and 53-120 is/are pending in the application.
- 4a) Of the above claim(s) 79-88 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 42-47, 50, 56-78, 89-97, 100, 101, 105, 107, 109, 111, 115-117 and 119 is/are rejected.
- 7) ☒ Claim(s) 53-55, 98, 99, 102-104, 106, 108, 110, 112-114, 118 and 120 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 April 2002 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>20031121, 20031222</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Examiner acknowledges Applicant's indication of withdrawn rejections and concurs with the same, except to the extent the 112 enablement rejection has been reinstated below.

Inventorship

In view of the papers filed 11/21/2003, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed from "AUGUSTINE M. K. CHOI, PATTY J. LEE, AND OTTERBEIN E. LEO" to "AUGUSTINE M. K. CHOI AND LEO E. OTTERBEIN." The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Specification

The disclosure is objected to because of the following informalities:

Please update cross-reference to related applications, indicating the current status of the related non-provisional application.

Specification, Pg. 7, "Figures" should "Drawings".

Specification, Pg. 7, "Figures 1 a and b" should be "Figures 1A and 1B" and "A" should be "Fig.1A" and "B" should be "Fig. 1B".

Specification, Pg. 8, "Figure 7 shows" should be "Figures 7A, 7B, 7C, 7D and 7E show" or, alternatively, "Figures 7A-7E show".

Specification, Pg. 8, "Figures 8a and 8b" should be "Figures 8A and 8B".

Specification, Pg. 8, "Figures 10 a and b" should be "Figures 10A and 10B".

Claims 53-55,98,99,102-104, 106,108,110,112-114,118, 120 are objected to as being dependent upon a rejected base claim.

Appropriate correction is required.

Drawings

The drawings are objected to because the pictures in Figures 2,9,11 are not clear. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-47,50,56-78,89-97, 100, 101, 105,107,109,111,115-117,119 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of inflammation with inhaled carbon monoxide as specifically set forth in the current (as of 11/21/2003) claims 53-55, 98,99,102,103,104,106,108,110,112,113,114, 118, 120, the Specification, does not reasonably provide enablement for treatment through other routes of administration or treatment of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims

The claimed invention does not appear to be currently recognized as a treatment for the various conditions and disease states in humans. Further, the working examples are limited to rats and the effects are observed either in lungs or on single cells, i.e. muscle cells or macrophages. It is asserted that the methods will treat a wide range of conditions and/or disease states; however, the disclosure does not appear to indicate what exactly is being treated, i.e., symptoms, underlying mechanisms, underlying disease, secondary problems associated with underlying disease, etc. Further, the conditions and disease states listed are in many cases not a single specific disease but represent a broad category of a number of disease having different etiologies, symptoms and/or treatments. Also, it appears that the active compounds are inhaled, however, other than the lungs there does not appear to be set forth in the disclosure how the compounds, in therapeutically effective amounts, reach the intended site be it kidneys, brain, heart, liver, spleen, skin, or systemically in general.

Finally, it is well-known that carbon monoxide is a deadly poison and that oxygen can cause pulmonary toxicity (Cecil Textbook of Medicine (2000), Vol. 1, pgs. 425-427). Concentrations of carbon dioxide, including concentrations falling within the claimed ranges are known to seriously impair oxygen hemoglobin binding capacity (The New Encyclopaedia Britannica (1994), Vol. 26 pg. 756). As such, the therapeutic window, if any, is extremely narrow. For instance, it has been suggested that excessive generation of carbon monoxide participates in the pathogenesis of Alzheimer's (Schipper et al., Abstract). Also, it is noted that the concentration of the gaseous components are claimed, however, concentration does not appear to adequately indicate how much of the gas is being administered and/or the effective amount of gas necessary to effect treatment. Clearly, flow rate and duration of administration

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effect the amount of gas administered and, consequently, the therapeutic and/or toxic effect on the patient. However, the disclosure, other than as specifically set forth in the examples, does not appear to indicate the flow rate and duration of administration or level of gas present in patient necessary to effect treatment relative to treatment of the claimed diseases and conditions (See The Merck Index, pg. 655, Asthma, O₂ Therapy). Examiner notes that current medications used in the treatment of the various disease states and/or conditions are not known to possess treatment efficacy for any and all symptoms, and in a number of conditions and/or disease states, treatment is limited to alleviating symptoms or slowing the progression of the disease without treating the disease itself (Cecil Textbook of Medicine (2000), Vol. 1, pgs. 273-279, 357-372, 387-419, 425-427, 436-448, 466-475, 507-512, 1060-1074; Cecil Textbook of Medicine (2000), Vol. 2, pgs. 1492-1499, 2042-2047, 2079-2081). As late as 1999, in a paper published by two of the inventors, the paper indicated that it may not be possible to prove that endogenous CO mediates the protective effects of HO-1 in vivo and there was only a possibility that inhalation of CO would be useful in other inflammatory disease states and that further experimentation was necessary. (Otterbein et al. (1999), pg. L693). See also Grau et al. (1992), pg. 423 (indicating that there is a great difference humans and rodents and that acute exposure to carbon monoxide increased tumor cell survival); Siow et al. (1999), pg. 388 (indicating that the effects of carbon monoxide on vascular smooth muscle relaxation are blood vessel and species specific, with findings differing from one study to another); Ringel et al. (1972), Abstract (indicating that exposure to carbon monoxide can cause parkinsonism); Schipper et al. (1995), Abstract (indicating that carbon monoxide may participate in the pathogenesis of Alzheimer's); and Stephens (1933), Abstract (indicating that exposure to carbon monoxide increased risk of

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occupational cancers). In light of the above, it is highly unlikely that administration of carbon monoxide would be effective for the treatment by of all the disease states or conditions set forth in the claims. As such, it appears that a skilled artisan would be required to do undue experimentation in order to make and/or use the invention commensurate in scope with the claims.

Examiner reinstates the above rejection based on the following:

Although Applicant has provided evidence that inhalation of carbon monoxide can treat or reduce inflammation as specifically set forth in the claims indicated above, Applicant has not shown how carbon monoxide can be effectively administered in other forms. Applicant has argued that modes of administration of gases to patients other than by inhalation are known in the art. However, none of the references cited involve the use of carbon monoxide and even if the references cited were sufficient to enable one to administer carbon monoxide, Applicant has not shown that other forms of administration would be effective in treating the various conditions or disease states. Applicant has argued with respect to Eschwey, which Applicant sites as a reference showing other forms of administration, “[g]iven that Eschwey’s complete lack of guidance regarding the biological activities and uses of carbon monoxide, and the generally known harmful effects of carbon monoxide at high concentrations, a skilled practitioner would have had no reason to expect such treatment to be successful”. (Remarks (2/3/2003), pgs. 18, 19).

Applicant has argued that retardation of growth was not sufficient to have taught a clinically useful approach to treating cancer (Remarks (11/21/2003, pgs. 19,20). As such, it cannot be said that the treatment of cancer as claimed is enabled by Applicant’s Specification.

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The only evidence provided by Applicant was from Application Serial No. 60/386,561 which only shows a reduction of tumor growth.

Claims 42-47,50,56-78,89-97, 105,107,109,111,115,117,119 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 42-47,50,56-78,89-97, 105,107,109,111,115,117,119 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in Paper No. 13 filed 2/3/2003. In that paper, applicant has stated "none of the publications cited in the Office Action, singly or in combination, teaches or suggests administering inhaled carbon monoxide gas as a therapeutic agent to treat the diseases and conditions recited in the pending claims" (pg. 20), and this statement indicates that the invention is different from what is defined in the claim(s) because the claims do not indicate that the carbon monoxide is administered by inhalation.

Examiner has duly considered Applicant's arguments but deems them unpersuasive.

Applicant argues that the quote was taken out of context, however, Applicant also argued in the response with respect to the 112 rejection that the Specification enables the treatment of various diseases/conditions with inhaled oxygen. Applicant's argument regarding the fact that it set forth inhalation in the dependent claims does not overcome the rejection. Applicant knew of said amendments, yet made the statements nonetheless. Applicant argues that at the time the application was filed, applicant's recognized, as would any skilled practitioner at that time, that gaseous compositions could be administered by patients in any number of ways. However, none of the references cited involve the use of carbon monoxide and even if the references cited were sufficient to enable one to prepare a non-gaseous formulation, Applicant has not shown that

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other forms of administration would be effective in treating the various conditions or disease states. In fact, Applicant has argued with respect to Eschwey, which Applicant sites as a reference showing other forms of administration, “[g]iven that Eschwey’s complete lack of guidance regarding the biological activities and uses of carbon monoxide, and the generally known harmful effects of carbon monoxide at high concentrations, a skilled practitioner would have had no reason to expect such treatment to be successful”. (Remarks (2/3/2003), pgs. 18, 19).

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 42-47, 50, 53, 62,65,67,104,108 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Otterbein et al. (March 1999).

Otterbein et al. (March 1999) expressly discloses methods of treating lung injury exhibited by lung airway and parenchymal inflammation, fibrin deposition and pulmonary edema by inhalation of 250 ppm, 0.025% carbon monoxide (Abstract).

Alternatively, at the very least the claimed invention is rendered obvious within the meaning of 35 USC 103, because the prior art discloses products and uses that contain the same exact ingredients/components as that of the claimed invention. See *In re May*, 197 USPQ 601, 607 (CCPA 1978). See also *Ex parte Novitski*, 26 USPQ2d 1389, 1390-91 (Bd Pat. App. & Inter. 1993).

Claims 42-47, 50, 53, 62,65,67,104,108 are also rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. Lin Mantell is listed as one of the authors, which includes the inventors, but is not listed as one of the inventors, as such, the cited reference contains a different inventive entity then the present application.

The rejection of Claim 61 under 35 U.S.C. 102(b) as being anticipated by Campbell (Abstract) is withdrawn for the reasons set forth in the response .

Claims 60,61, 90-95, 100,101,116,117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maxwell et al. (Abstract) in view of Campbell (Abstract).

Maxwell et al. teach that exposure of animals bearing transplantable tumors to carbon monoxide resulted in a decrease in the rate of tumor growth.

Campbell teaches that inhalation of carbon monoxide retarded development of cancer of the skin and primary adenoma of the lungs in mice.

The difference between the claimed invention and the prior art is that the prior art does not expressly disclose the treatment of cancer in a human patient by administering inhaled carbon monoxide. However, the prior art amply suggests the same as it is known that it is effective in the treatment of cancer in animals. As such, it would have well within the skill of

and one of ordinary skill in the art would have been motivated to use the same in humans with the expectation that inhaled carbon monoxide would be effective in treating cancer in humans.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Examiner has duly considered Applicant's argument but deems them unpersuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The fact that a number of mice died due to carbon monoxide exposure is not sufficient to overcome the rejection as it is well within the skill of one of ordinary skill to use amount of carbon monoxide which are sublethal as evidenced by the Maxwell reference. Applicant argues that because Maxwell only shows retardation of growth and there are side effects that it would likely be unacceptable as clinical treatment in any animal, much less humans. However, the mere fact that there are adverse effects of treatment is not sufficient to preclude the clinical use of a drug. If this were true, then no drug, especially, such potent drugs as are currently used for treatment of cancers would not be used much less have been developed for use. Clearly, it is within the skill of one of ordinary skill in the art, for example a physician, to modify doses depending on efficacy and toxicity. Applicant argues that Maxwell only shows reduction of tumor growth, however, Applicant submitted evidence of reduction of tumor growth which according to Applicant was sufficient to support claims treating cancer.

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Conclusion

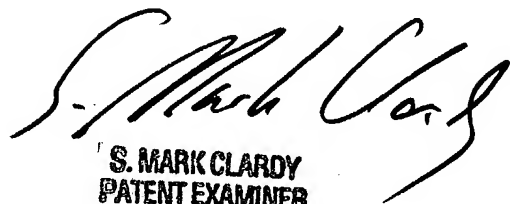
A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a flexible schedule. However, Examiner may generally be reached Monday-Friday, 8:00 am – 5:30 pm (EST), except the first Friday of the each biweek which is Examiner's normally scheduled day off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. Thurman Page, can be reached at (571)272-0602). Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (703) 308-1235 and (703) 308-0198, respectively.

FIC

February 19, 2004



S. MARK CLARDY
PATENT EXAMINER
GROUP 1200
1616